A review of Group B Streptococcus maternal-fetal infection

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SUMMARY
For a long time, infectious diseases have been a major public health problem, mainly maternal fetal infections linked to neonate’s mortality. Streptococcus agalactiae (GBS) infection is one of the main infections, which threat mother-infant health. One of the major challenges that remains to be addressed is therapeutic care strategy, further, the emergence of antibiotic resistant bacteria which constitute a major challenge for clinicians. Concerning GBS an antibiotic prophylaxis regimen is adopted to reduce the vertical transmission of bacteria from mother to neonate and avoid the appearance of complications related to GBS infection such as early onset disease and late onset disease that can lead to stillbirths. Like most bacteria, GBS is susceptible to first-line antibiotics, and in case of resistance, therapy is based on second and third-line antibiotics. The drug susceptibility testing of microorganisms is therefore essential in the therapeutic strategy, because it not only facilitates the orientation of treatment but also help to set up a system supervising the expansion of resistant strains. This present paper constitutes a literature review on Streptococcus agalactiae maternal-fetal infection and summarizes some epidemiological studies on the emergence of this bacterium as well as it provides the prevalence of its resistance to antibiotics and outlines some vaccine development strategies.

Introduction
Maternal-fetal infections represent a major public health problem in the world. These infections are mostly due to bacterial agents, mainly Streptococcus agalactiae, Escherichia coli and Listeria monocytogenes.
Streptococcus is a group of micro-organisms which contains many species. Group B Streptococcus (GBS); *Streptococcus agalactiae*, formerly *Streptococcus mastitidis* because of its association with bovine mastitis (Sherman, 1937). It is a coccobacillus gram positive bacteria, composed of cocci arranged in chains, colonizing gastrointestinal and urogenital tracts. GBS was identified in the 1930s by Rebecca Lancefield. It is a frequent cause of maternal fetal and neonate’s diseases, and considered as the first cause of septicemia in neonates, further, it causes pneumonia and meningitides. It is able to induce immune complications and mortality in adults (Hanna and Noor, 2021).

**History**

The history began in 1879, when Louis Pasteur isolated a group of microorganisms arranged in chains of four or more, from women with puerperal fever. Then, he linked its presence and its related disease to the increase of mortality in newborns and women. In 1884, Rosenbach gave them the name of Streptococci. Over the years, many changes have been occurred to the nomenclature and classification of Streptococci. First, the classification of Streptococci into two groups; Streptococcus haemolyticus and Streptococcus viridans was based on hemolytic properties after streaking them on blood agar by Schottmuller in 1903. Thereafter, in 1919 Brown classified them into three groups: Alpha, Beta and Gamma. In 1933, another type of classification by the expression of beta-hemolysis on blood agar based on immunological approaches and antigenic properties was established by Lancefield to classify Streptococcus haemolyticus into various groups by using precipitin reaction. Therefore, Group B Streptococci represent strains isolated from bovine. While Group A strains are isolated from human diseases and Group C strains from other animals. Lancefield’s classification is mostly considered as a system involved in the identification of Streptococci (Lancefield, 1933). It is divided into nine serotypes, then into ten (Ia, Ib, II, III, IV, V, VI, VII, VIII, IX) depending on the capsular polysaccharide (Edwards and Baker, 2005). Another classification was constructed by Sherman in 1937, according to hemolytic reaction into four division categories; the pyogenic division, the viridan division, the lactic division, and the enterococci (Facklam, 2002). Over the years, these studies in addition to others, allowed defining groups and individualizing Streptococcus species using different taxonomic criteria.

**Epidemiology**

*Streptococcus agalactiae* is a frequent cause of severe and invasive infections in newborns, pregnant women and adults. In 1935, Lancefield and Hare reported the relationship between the presence of group B Streptococcus and uterus infections, some of which were fatal after childbirth (Sherman, 1937). Different serotypes of GBS have been identified as causing human disease; Ia, Ib, II, III and V, with different severity and different distribution (Gibbs et al., 2004).

GBS infection remains the main cause of bacterial infection newborns; it leads to two type of complications EOD (early onset diseases; occurring from day 0 to 6 of life) and LOD (late onset disease; occurring from day 7 to 90 of life) it represents 30 to 40% of neonatal bacterial infections (VANCLAIRE et al., 1993).

The worldwide frequency of GBS vaginal carrier is of the order of 5 to 40%. As usual, bacterial infections present a geographic variation. Further, African-American race is considered as one of risk factor for GBS infection associated disease (Gibbs et al., 2004).
Whereas other studies report that the range of colonization in developing countries is similar to that reported in the United States (Stoll and Schuchat, 1998).

This is due to a rarely identification of this pathogen in developing countries. According to what is reported by Stoll, the global colonization rate is about 12.7% and he indicates the existence of a difference between studies in terms of the use of adequate methods or not.

Taking into account studies using adequate methods only the prevalence in Middle East/North Africa, Asia/Pacific, Sub-Saharan Africa, India/Pakistan, Americas is 22%, 19%, 19%, 12%, 14% respectively (Stoll and Schuchat, 1998).

In 2016, almost the same statistics have been reported in a bibliography review published by Kwatra, 17.9% as a global prevalence of colonization by group B Streptococcus. He demonstrated the existence of a regional heterogeneity between countries such as Southeast Asia, Europe, America and Africa with rates 11.1%, 19%, 19.7%, 22.4% respectively (Kwatra et al., 2016).

There is such difference in serotype distribution causing infant diseases; as it is reported by Madrid L. et al. the most dominant GBS serotype is serotype III (61.5%) followed by Ia (19.1%), V (6.7%) and Ib (5.7%) (Madrid et al., 2017).

In 2017, Russell et al. reported that the prevalence of GBS colonizing pregnant women worldwide is around 18% (Russell et al., 2017).

**Structure**

The structure of GBS like most Gram-positive bacteria gives it a certain pathogenicity and virulence due to a specific component. As mentioned before GBS is divided into several serotypes depending on the capsular polysaccharide (CPS). It constitutes a major virulence factor by playing a crucial role in escaping host defense mechanisms (Morach et al., 2018). It gives it the ability to survive within the host, through different mechanism; either by masking antigenic determinants associated with the bacterial surface, mimicking host antigens or interfering with complement-mediated killing (Cieslewicz et al., 2005).

GBS expresses other factors such as a pore-forming protein toxin (CAMP factor, β-hemolysin), resistance to antimicrobial peptides (AMPs) factor (Penicillin-binding protein PBP), host-cell adherence factors (Fibrinogen-binding protein A and B (FbsA, FbsB), Laminin-binding protein Lmb,…). The pore-forming toxins play a key role in the entry and dissemination of the pathogen into host cells, as well as its intracellular survival by forming pores in host-cell membrane (Rajagopal, 2009). Others GBS factors act on immune defenses, such C5a peptidase encoded by scpB gene. It mainly targets neutrophils recruitment by cleaving C5a which is an important element in neutrophil recruitment to the site of infection (Six et al., 2014).
Table 1 Streptococcus agalactiae colonization rates in pregnant women.

<table>
<thead>
<tr>
<th>Region/country of study</th>
<th>Study period</th>
<th>Type of study</th>
<th>Streptococcal carriage</th>
<th>Study authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>1st January-31st August 2002</td>
<td>Retrospective</td>
<td>23.7%</td>
<td>Lorquet et al., 2005</td>
</tr>
<tr>
<td>Tunisia</td>
<td>March-May 2005</td>
<td>Prospective</td>
<td>12.92%</td>
<td>Jerbi et al., 2007</td>
</tr>
<tr>
<td>Morocco (Fez)</td>
<td>1st April 2009-31th March 2010</td>
<td>Prospective</td>
<td>23.3%</td>
<td>Mahmoud et al., 2011</td>
</tr>
<tr>
<td>Sandi Arabia</td>
<td>September 2013-December 2014</td>
<td>Prospective</td>
<td>13.4%</td>
<td>Khan Mobashir et al., 2015</td>
</tr>
<tr>
<td>Morocco (Rabat)</td>
<td>March-July 2013</td>
<td>Prospective</td>
<td>24%</td>
<td>Morealesa et al., 2018</td>
</tr>
<tr>
<td>Ghana</td>
<td>May-September 2013</td>
<td>Prospective</td>
<td>19.1%</td>
<td>Vinnamiere et al., 2015</td>
</tr>
<tr>
<td>Morocco (Marrakesh)</td>
<td>June 2012-December 2012</td>
<td>Prospective</td>
<td>20.2%</td>
<td>Bassir et al., 2016</td>
</tr>
</tbody>
</table>

**Treatment**

The treatment most often given to newborns and women for streptococcal infections is antibiotics.

Beta-lactams and aminoglycosides (gentamicin) are currently the standard first line treatment for this type of infection. Beta-lactams exert a blocking effect on the action of enzymes involved in cell wall synthesis, such as penicillin exert an inhibiting effect on peptidoglycan formation by binding the beta-lactam ring to penicillin binding proteins (PBP), causing cell death because of the imbalance in cell wall maintenance. Gentamicin is recommended to treat severe invasive infections due to GBS in combination with penicillin (Hayes et al., 2020).

GBS remains sensitive to beta-lactams, especially penicillin G, ampicillin, carbapenems and cephalosporin. On the other side, this therapy could have a low efficacy due to different factors and it could be substituted with an alternative therapy using clindamycin, fluoroquinolones, erythromycin and vancomycin (Raabe and Shane, 2019).

Despite an increased resistance to clindamycin and erythromycin among GBS isolates in the 1990s has been observed (Gibbs et al., 2004).

Antibiotic prophylaxis should be intravenous, because it has been demonstrated that it reduces vertical transmission of GBS as well as it prevents the occurrence of early-onset neonatal diseases and maternal morbidity.

According to The American Academy of Pediatrics, therapeutic strategy should be administered at least 4 hours before delivery to achieve sufficient concentration of ampicillin or penicillin G in the amniotic fluid and in placenta circulation, and then it may reduce the rate of GBS and its transmission (Newborn, 1992).

**Antibiotic resistance**

Antibiotic resistance is considered as a significant health problem. It is mainly due to the excessive and uncontrolled use of antibiotics, as well as to self-medication and over-prescription. This has led to the decrease in efficacy or even the ineffectiveness of the treatment regimens. Usually, beta-lactams are used as a first line therapy; in case patients showing an allergic reaction to penicillin, a second line (erythromycin and clindamycin) or third line (vancomycin) therapy is administered. However, reports of reduced susceptibility to penicillin are becoming more prevalent (Hayes et al., 2020).

Beta-lactam resistance can be due to antibiotic destruction by beta-lactamases, reduced binding affinity or reduced
access to Penicillin-binding proteins (PBPs) (Hayes et al., 2020).

In some cases, antibiotic resistance can be worse than just reduce treatment efficacy and even lead to mortality cases. In 2015, Cassini et al. estimated the number of attributable deaths linked to antibiotic resistance, around 33 110 deaths registered as result of antibiotic resistance from European Antimicrobial Resistance Surveillance Network (EARS-Net) data in 30 countries in European Union and European Economic Area (Cassini et al., 2019).

Ben Hamida recorded a high susceptibility of GBS to ampicillin estimated to 96.7%. Drug susceptibility testing analysis allowed defining resistance of GBS to erythromycin about 40% of cases; while 96.7% of GBS were susceptible to ampicillin (Ben Hamida Nouaili et al., 2011).

One Japanese study reported the increased incidence of GBS reduced penicillin susceptibility rate, increasing from 2.3% in 2005–2006 to 14.7% in 2012–2013 (Seki et al., 2015). Regarding erythromycin resistance, different results were reported among studies; a Chinese study showed that the erythromycin-resistance is particularly high, with rate of 74.1% observed in both colonizing and invasive isolates (Lu B et al., 2016). Also in Beijing, Wang et al. reported a high rate of macrolide resistance; the non-susceptibility rate reported for erythromycin is around 85.7% (Wang et al., 2015). While, an Italian study reported a slightly low rate of erythromycin resistance in the studied population that was estimate to about 43.75% (Matani et al., 2016). Lower rate has been registered in Ghana 1% (Vinnemeier et al., 2015). Resistance to macrolide antibiotics (erythromycin) is due to various mechanisms including efflux pumps, ribosomal modification (methylation via methyl-transferases encoded by erm gene), and drug inactivation by enzymatic modification of antibiotics (Hayes et al., 2020). As for resistance to aminoglycosides, a French study reported a high level of resistance especially for amikacin around 8.8%, and 0.3% were resistant to gentamicin (Hays et al., 2016).

**Vaccine**

Currently, GBS vaccine is under development, whereas, no vaccine is actually available and licensed. It constitutes the unique preventive strategy to fight against the propagation of this type of infection threatening the mother-child health axis.

World Health Organization considers the development of a GBS vaccine for pregnant women as a priority. A new report from the World Health Organization (WHO) and the London School of Hygiene & Tropical Medicine (LSHTM) shows the alarming global impact of GBS.

In this report, an urgent call is made for the development of maternal GBS vaccines to reduce these rates, noting that these could be very cost-effective but it will have significant benefits for maternal-fetal health (WHO, 2021).

As mentioned above, Streptococcus agalactiae is classified into various serotypes depending on the expression of capsular polysaccharide, so most GBS vaccines in development target this structure; therefore, they may only be effective against some strains (Hayes et al., 2020). Other vaccination strategies are under investigation targeting surface proteins, even they are not conserved through all strains (Furfaro et al., 2018). Also, GBS virulence factors are studied as potential vaccine candidates as well as sialic acid-rich capsular polysaccharide (CPS) which plays a key role in host immune defense mechanisms and biofilm formation. Polysaccharides are conjugated to other carrier proteins to trigger an effective protective response and an active memory B-cell response. Conjugated vaccines using CPS and carrier proteins showed better results compared to unconjugated vaccines (Carreras-Abad et al., 2020).
Some studies on alternative vaccine using proteins have revealed some surface proteins which are expressed by different serotypes and they can be used as a target for alternative vaccine; such as the Alpha-Like Protein (Alp) family proteins (AlphaC, Alp1, Alp2, Alp3, Alp4 and Rib), C5a peptidase, the latch-peptide, pilus protein (Carreras-Abad et al., 2020).

The prevention strategy is based on prenatal screening test for GBS in the vagina or rectum of pregnant women between 35 and 37 weeks of pregnancy. Then, pregnant women with GBS, symptomatic or not, should be treated and receive an intrapartum antibiotic prophylaxis (CDC, 2021).

**Conclusion**

The streptococcal B infections are one of major public health problem, its severity remains in vertical maternal fetal transmission which leads to sever complications and high rates of mortality in spite of care measures. It is therefore necessary to increase efforts in terms of prenatal prevention and to make decisions about early diagnosis, antibiotic therapy and prevention strategies, knowing that the synthesis of a vaccine providing effective immunity against all GBS serotypes remains a difficult problem.

Thus, it is important to put a prevention and management strategy for the sustainable control of maternal and neonatal morbidity and mortality due to infections on longitudinal and integrated prospective studies.

**Conflicts of Interest**

There is no conflict of interest.

**References**

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